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(54) Title: FOAMS FOR DELIVERY OF MINOXIDIL

(57) Abstract

Novel, slow- and quick-breaking foams containing minoxidil. These foams provide a pharmaceutically elegant means for the topical delivery of this compound.

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FOAMS FOR DELIVERY OF MINOXIDIL

DESCRIPTION

The present application provides a new composition for administration of known pharmaceutical compounds. In particular, the present invention provides: aerosol and non-aerosol quick-breaking and slow-breaking foams for the topical delivery of minoxidil and related compounds.

Minoxidil, or 2,4-pyrimidinediamine, 6-(1-piperidinyl)3-oxide, is a potent vasodilator sold under the trademark LONITEN® Tablets for use in the treatment of hypertension. It is also useful as a topically applied hair growth agent for the treatment of baldness. Topical minoxidil is administered in a topical composition containing propylene glycol, ethanol and water.

U.S. Patent 4,139,619 claims topical compositions of minoxidil and related 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-2-iminopyrimidines as well as the use of such compositions for (a) increasing the rate of growth of terminal hair, and (b) converting growth of vellus hair to growth as terminal hair. U.S. Patent 4,596,812 also discloses certain topical minoxidil compositions as well as their use as therapeutic agents to treat human alopecia and arrest and reverse male pattern alopecia.

There are many different types of hair loss, the most common being "alopecia" wherein human males begin losing scalp hair at the temples and on the crown of the head as they get older. While this type of hair loss is largely confined to males, hence its common name "male pattern baldness", it is not unknown in women. Hair loss can be seen as gradual hair conversion.

Terminal hairs are coarse, pigmented, long hairs in which the bulb of the hair follicle is seated deep in the dermis. Vellus hairs are fine, thin, non-pigmented short hairs in which the hair bulb is located superficially in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

INFORMATION DISCLOSURE

U.S. Patent 4,139,619 discloses topical minoxidil compositions containing carriers selected from ointments, lotions, pastes, jellies, sprays, and aerosols. U.S. Patent 4,596,812 also discloses

topical compositions of minoxidil.

SUMMARY OF THE INVENTION

The present invention particularly provides

(1) a topical composition for application to mammalian skin comprising:

(a) minoxidil in an amount from about 1 to about 5% on a weight to weight basis (%w/w);

(b) propylene glycol in an amount from about 10 to about 50% w/w;

(c) alcohol in an amount from about 30 to about 75% w/w;

(d) an emulsifier and/or surfactant in an amount from about 0.5 to about 10% w/w;

(e) hydroxypropyl methylcellulose in an amount from about 0.1 to 0.5% w/w; and

(f) water in an amount from about 10 to about 50% w/w;

(2) the above composition wherein composition is actuated using a propellant;

(3) the above composition wherein the composition is actuated using a hydrocarbon, chlorofluorocarbon P-12 or an approximately 40:60 mixture of chlorofluorocarbon P-12 and P-114 in a range of about 2.5 to about 25% w/w;

(4) the above composition wherein the following amounts are employed:

Components	% w/w
Minoxidil	2
Propylene glycol USP	20
Alcohol USP	53
Polawax	4
Hydroxypropyl methylcellulose USP	0.1
Purified water USP	20;

(5) a topical composition for application to mammalian skin comprising the following components, in a range on a weight to weight basis (% w/w):

(a) minoxidil in an amount from about 1 to about 3% on a weight to weight basis (%w/w);

(b) 1,3 butylene glycol in an amount from about one to about 30% w/w;

(c) a glycol in an amount up to about 50% w/w;

(d) alcohol in an amount up to about 20% w/w;

(e) a surfactant and/or emulsifier and/or fatty alcohol and/or fatty alkanolamide in an amount from about 0.1 to about 15% w/w;

(f) film former in an amount up to about 5% w/w;

with the remainder of the composition being water; and

(g) a skin penetrant in an amount up to about 20%;

with the proviso that the composition contain at least 10% of components b-c, at least 15% of components b-d and at least 0.1% of components e-g;

(6) the above composition wherein the composition is actuated by a propellant;

(7) the above composition wherein the propellant is chlorofluorocarbon P-12 or a suitable hydrocarbon in the range of about 1-15% w/w;

(8) the above composition having the following components:

Components	% w/w
Minoxidil	2.0
Propylene glycol	25.0
1,3 Butylene glycol	30.0
Alcohol USP	2.15
Polyvinyl pyrollidone and vinyl acetate	4.5
Cocamidopropyl betaine	1.0
Polyoxyethylene 23 lauryl ether	5.0
Purified water	56.65;

(9) a composition selected from the following compositions, comprising the following components:

(a)

Components	% w/w
Polawax A.31 (emulsifying wax NF ethoxylated stearyl alcohol with emulsifying agents)	2.0
Alcohol USP	15.0
Propylene glycol	10.0
1,3 Butylene glycol	30.0
Hydroxypropylmethylcellulose	0.2
Minoxidil	2.0
Purified water	42.8;

(b)	Components	% w/w
	Propylene glycol	25.0
	Alcohol USP	20.0
	Polyoxyethylene 23 lauryl ether	5.0
	Minoxidil	2.0
	Purified water	48.0;

(c)	Components	% w/w
	Propylene glycol	30.0
	Alcohol USP	20.0
	Minoxidil	2.0
	POE (23) lauryl ether	0.5
	POE (2) stearyl ether	0.5
	Cocamidopropyl betaine	0.5
	Isostearyl alcohol	0.5
	Purified water	46.0;

(d)	Components	% w/w
	Propylene glycol	30.0
	Alcohol USP	20.0
	Minoxidil	2.0
	Oleth-10	2.0
	Purified water	46.0;

(e)	Components	% w/w
	Propylene glycol	50.0
	Alcohol USP	20.0
	Minoxidil	5.0
	POE (23) lauryl ether	0.5
	POE (2) stearyl ether	0.5
	Cocamidopropyl betaine	0.5
	Isostearyl alcohol	0.5
	Purified water	23.0;

(f)	Components	% w/w
	Propylene glycol	50.0
	Alcohol USP	20.0
	Minoxidil	5.0
	Oleth-10	3.0
	Cocamidopropylbetaine	1.0
	Purified water	21.0; and

(g) Components	% w/w
Propylene glycol	10.0
Butylene glycol	15.0
Alcohol USP	20.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Isostearyl alcohol	0.5
Minoxidil	2.0
Purified water	50.0.

Surprisingly and unexpectedly, the novel foam compositions provided herein provide a pharmaceutically elegant means of topically administering minoxidil. In addition, certain of the compositions provided herein greatly increase skin penetration as compared to the propylene glycol/ethanol/water compositions of the prior art.

The use of topical minoxidil compositions, including the compositions of the present invention in the treatment and prevention of baldness is well known to an ordinarily skilled physician or dermatologist. In addition, this use is set forth in U.S. Patents 4,139,619 and 4,596,812, which patents are expressly incorporated by reference herein.

The aerosolized formulation is a homogeneous, aqueous-alcoholic emulsion system. The aerosolized formulation upon actuation produces a stabilized, homogeneous, expandable foam which breaks easily with shear. A composition of this type is sometimes referred to as a "mousse".

By "minoxidil" is meant the compound named 2,4-pyrimidine-diamine, 6-(1-piperidinyl)-3-oxide, as well as analogs salts thereof, as described in U.S. Patents 4,139,619 and 4,596,812, which patents are incorporated by reference herein.

Suitable glycols include propylene glycol, 1,3-butylene glycol, propylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400) hexylene glycol, and dipropylene glycol.

Suitable skin penetrants include alcohols such as dodecanol and oleyl alcohol; amines, such as isopropyl amine, diisopropyl amine, triethyl amine, triethanol amine, diisopropanolamine and ethylene diamine; carboxylic acids, such as oleic acid, linoleic acid and linolenic acid; esters, such as dibutyl sebacate, dibutyl phthalate, butyl benzoate and ethyl caprate; and others, such as Azone®, N

methyl pyrollidone, bile salts and urea.

All of the compositions herein may be actuated using propellants known to those of ordinary skill in pharmaceutical or cosmetic formulations. Such propellants include hydrocarbons such as propane, isobutane or dimethyl ether and chlorofluorocarbons such as P-12, P114, and a 40:60 mixture thereof.

By alcohol is meant any of the common alcohols used in conventional pharmaceutical or cosmetic foam compositions including ethanol, isopropanol, and the like.

By emulsifier and/or surfactant is meant any of the known agents for modifying the surface tension of a composition and making an emulsion more stable, such as Polawax regular, Polawax A-31, cocamidopropyl betaine, polyoxy ethylene (POE) 23 lauryl ether, and polyoxyethylene (POE) 2 stearyl ether. Included in the class of emulsion stabilizers are the long chain fatty alcohols and fatty alkanolamides such as lauryl alcohol, isostearyl alcohol, and cocamide DEA.

By film former is meant a high molecular weight polymer such as a cellulose derivative or resin. Hydroxypropyl methylcellulose and polyvinyl pyrollidone and vinylacetate are typical examples.

Small amounts of other components may be added to the composition, e.g., perfumes, color additives, and the like. In particular, the addition of surfactants Span 60 and Tween 80, in ranges of 0.5 to 10% w/w, preferably 3% w/w, is desirable to improve the physical stability of the formulation.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is seen more fully by the Examples given below.

Example 1

Alcohol and propylene glycol are heated to 50-60°C and minoxidil is added and mixed until dissolved. In a separate container Polawax is heated until melted (approximately 50-60°C). To a third container of water, heated to 50-60°C, is added hydroxypropylmethyl cellulose, and mixing is continued until the dispersion is complete. The alcohol and Polawax mixtures, are homogenized using a homogenizer, and the aqueous phase is added and this total mixture is homogenized.

All three mixtures are maintained at about 50-60°C during this mixing process. After mixing, the mixture is cooled to about 40°C

and added to an aerosol vial to which a propellant is added.

Using this procedure, and the appropriate amounts of starting materials, a composition containing the following percentages of components is prepared:

Components	% w/w
Minoxidil	2
Propylene glycol USP	20
Alcohol USP	53
Polawax Regular	4
Hydroxypropyl methylcellulose USP	1
Purified water USP	20

The resulting foam is quick-breaking and pharmaceutically elegant.

Using analogous procedures, and the appropriate starting materials, all of the compositions of Claim 1 are prepared.

Example 2

Procedure A

Minoxidil is dissolved in a glycol mixture. To a separate container is added POE (23) lauryl ether and POE (2) stearyl ether, lauryl alcohol, and purified water, and the mixture is heated to a temperature to dissolve the waxes. The two mixtures are combined with agitation and cooled to room temperature. Using this procedure, and the appropriate amounts of starting materials, a composition containing the following percentages of components is prepared:

Components	% w/w
Propylene glycol	10.0
Butylene glycol	30.0
POE (23) lauryl ether	1.8
POE (2) stearyl ether	1.2
Lauryl alcohol	0.9
Minoxidil	2.0
Purified water	53.5

The resulting composition, upon actuation, is a stiff, slow-breaking foam.

Procedure B

Oleyl alcohol is heated to about 60°C. In a separate container water, POE (2) stearyl ether, and POE (23) lauryl ether are combined and heated to about 60°C, with stirring. Minoxidil is added to butylene glycol and water and the mixture is stirred until the

minoxidil is dissolved. The two mixtures are combined and the resulting mixture stirred until cooled to room temperature.

Using this procedure, and the appropriate amount of starting materials, a composition containing the following amounts of components is prepared:

Components	% w/w
Oleyl alcohol	15.0
POE (2) Stearyl ether	8.0
POE (23) Lauryl ether	2.0
Purified water	30.0
Butylene glycol	15.0
Minoxidil	1.0
Purified water q.s.	100

The resulting composition, upon actuation, produces a stiff, creamy, slow-breaking foam.

Example 3

Minoxidil is dissolved in propylene glycol and heated with mixing to 72°C. Dissolve the POE (23) lauryl ether in the purified water and heat to 72°C with mixing. In a separate container, combine and mix the POE (2) stearyl ether and the isostearyl alcohol while heating to 70°C. Combine the minoxidil and POE (23) lauryl ether solutions with mixing while maintaining at 72°C. Add the POE (2) stearyl ether-isostearyl alcohol mixture to the minoxidil solution with rapid agitation. Continue mixing until cooled to room temperature. Add the alcohol and mix until uniform.

Using this procedure, and the appropriate amount of starting materials, a composition containing the following amounts of components is prepared.

Components	% w/w
Propylene glycol	30.0
Alcohol USP	20.0
Minoxidil	2.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Cocamidopropyl betaine	0.5
Isostearyl alcohol	0.5
Purified water	46.0

The resulting foam is pressure-sensitive, slow breaking and

pharmaceutically elegant.

Example 4

Minoxidil is dissolved in propylene glycol and heated with mixing to 72°C. The oleth-10 is combined with the purified water and heated with mixing to 72°C. The oleth-10 solution is added to the minoxidil solution with continued mixing while cooling to room temperature. Add the alcohol and mix until uniform.

Using the procedure and the appropriate amount of starting materials, a composition containing the following amounts of components is prepared:

Components	% w/w
Propylene glycol	30.0
Alcohol USP	20.0
Minoxidil	2.0
Oleth-10	2.0
Purified water	46.0

The resulting foam is pressure-sensitive, slow-breaking and pharmaceutically elegant.

Example 5

Using the procedure described in Example 3, and the appropriate amount of starting materials, a composition containing the following amounts of components is prepared:

Components	% w/w
Propylene glycol	50.0
Alcohol USP	20.0
Minoxidil	5.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Cocamidopropyl betaine	0.5
Isostearyl alcohol	0.5
Purified water	23.0

Note: The cocamidopropyl betaine is added to the POE (23) lauryl ether and purified water, then heated to 72°C with mixing.

The resultant foam is pressure-sensitive, slow-breaking and pharmaceutically elegant.

Example 6

Using the procedure described in Example 4,and the appropriate amount of starting materials, a composition containing the following

amounts of components is prepared:

Components	% w/w
Propylene glycol	50.0
Alcohol USP	20.0
Minoxidil	5.0
Oleth-10	3.0
Cocamidopropyl betaine	1.0
Purified water	21.0

Note: The cocamidopropyl betaine is added to the purified water with the oleth-10, then heated with mixing to 72°C.

Example 7

The propylene glycol, butylene glycol, POE (23) lauryl ether, minoxidil and purified water are combined and heated with mixing to 72°C. The POE (23) stearyl ether and isostearyl alcohol are combined and heated with mixing to 70°C, then added to the aqueous solution with rapid agitation. Mixing is continued while cooling to room temperature. Add the alcohol and mix until uniform.

Using this procedure, and the appropriate amount of starting materials, a composition containing the following amounts of components is prepared:

Components	% w/w
Propylene glycol	10.0
Butylene glycol	15.0
Alcohol USP	20.0
POE (23) lauryl ether	0.5
POE (2) Stearyl ether	0.5
Isostearyl alcohol	0.5
Minoxidil	2.0
Purified water	50.0

Using these and analogous procedures, all of the compositions of Claim 5 are prepared.

Example 8

The following hairless mouse skin transport studies were conducted on compositions prepared as in Example 1. For comparison, formulations were also tested which contain 25% and 30% water. In addition, a comparison study was run utilizing a formulation containing 30% water applied as the aerosolized foam and also as the non-aerosolized gel.

For each composition, radiolabelled formulations of minoxidil were applied to the surface of 5 hairless mouse skins (Franz cell apparatus) and transport through the stratum was corneum monitored. Permeability coefficients and lag times for the absorption of minoxidil through the skin were calculated.

Minoxidil Topical Foam 2% (25% water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	1.187 x 10-7	2.146
2	101.922 x 10-7	1.895
3	2.470 x 10-7	2.107
4	2.332 x 10-7	1.658
5	1.494 x 10-7	1.825
Ave:	1.881 x 10-7	1.926

Minoxidil Topical Solution 2%

Cell#	Pe (cm/sec)	T (lag) (hr)
1	2.164 x 10-8	3.521
2	3.141 . 10-8	4.745
3	2.267 x 10-8	2.782
4	1.503 x 10-8	4.421
5	2.703 x 10-8	4.254
Ave:	2.355 x 10-8	3.944

Minoxidil Topical Foam 2% (30% Water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	1.590 x 10-8	1.001
2	2.730 x 10-8	1.258
3	2.840 x 10-8	1.675
4	2.114 x 10-8	3.611
5	3.440 x 10-8	3.120
Ave:	2.543 x 10-8	2.133

Minoxidil Topical Foam 2% (20% Water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	5.908 x 10-8*	1.504
2	2.373 x 10-7	2.142
3	1.209 x 10-7	3.109
4	1.384 x 10-7	1.881
5	1.130 x 10-7	2.618
Ave:	1.524 x 10-7 Ave (4):	2.251

* Data excluded from average

Minoxidil Topical Solution 2%, (20% Water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	1.425 x 10-8	3.120
2	1.575 x 10-8	2.514
3	1.760 x 10-8	3.383
4	1.244 x 10-8	3.029
5	1.511 x 10-8	2.191
Ave:	1.511 x 10-8	2.847

Minoxidil Topical Foam 2% (30% Water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	1.012 x 10-7*	4.021
2	6.400 x 10-8	3.261
3	5.297 x 10-8	4.144
4	3.500 x 10-8	3.952
5	3.240 x 10-8	4.899
Ave:	4.608 x 10-8 Ave (4):	4.055

* Data excluded from average

Minoxidil Topical Gel 2% (30% Water)

Cell#	Pe (cm/sec)	T (lag) (hr)
1	1.034 x 10-7	4.129
2	1.325 x 10-7	3.611
3	2.180 x 10-7	3.217
4	1.653 x 10-7	3.217
5	1.686 x 10-7	3.034
Ave:	1.576 x 10-7	3.361

As can be seen, the minoxidil foams of Example 1 greatly increased the transport of minoxidil through the skin 10 fold as compared to the propylene glycol-ethanol-water formulations of the prior art.

CLAIMS

1. A topical composition for application to mammalian skin comprising:

(a) minoxidil in an amount from about 1 to about 5% on a weight to weight basis (%w/w);

(b) propylene glycol in an amount from about 10 to about 50% w/w;

(c) alcohol in an amount from about 30 to about 75% w/w;

(d) an emulsifier and/or surfactant in an amount from about 0.5 to about 10% w/w;

(e) hydroxypropyl methylcellulose in an amount from about 0.1 to 5% w/w; and

(f) water in an amount from about 10 to about 50% w/w.

2. A composition of Claim 1, wherein the composition is actuated using a propellant.

3. A composition of Claim 1, wherein the chlorofluorocarbon P-12 or an approximately 40:60 mixture of chlorofluorocarbon P-12 and P-114 in a range of about 10 to about 20% w/w, or a hydrocarbon in the range of 10 to 30% w/w.

4. A composition of Claim 3, wherein the following amounts are employed:

Components	% w/w
Minoxidil	2
Propylene glycol USP	20
Alcohol USP	53
Polawax	4
Hydroxypropyl methylcellulose USP	1
Purified water USP	20

5. A topical composition for application to mammalian skin comprising the following components, in a range on a weight to weight basis (% w/w):

(a) minoxidil in an amount from about 1 to about 5% on a weight to weight basis (%w/w);

(b) 1,3 butylene glycol in an amount up to about 30% w/w;

(c) propylene glycol in an amount up to about 50% w/w;

(d) alcohol in an amount up to about 25% w/w;

(e) surfactant and/or emulsifier and/or fatty alcohol and/or fatty alkanolamide in an amount up to about 15% w/w;

(f) film former in an amount up to about 5% w/w; and

(g) skin penetrant in an amount up to about 20% w/w;

with the remainder of the composition being water;

with the provisos that the composition contain at least 5% of components b-c, at least 15% of components b-d and, at least 0.1% of components e-g.

6. A composition of Claim 5, wherein the composition is actuated using a propellant.

7. A composition of Claim 5, wherein the propellant is a hydrocarbon or chlorofluorocarbon in the range of about 1 to 20% w/w.

8. A composition of Claim 5 comprising the following components:

Components	% w/w
Minoxidil	2.0%
Propylene glycol	25.0%
1,3 Butylene glycol	30.0%
Alcohol USP	2.15
Polyvinyl pyrollidone and vinyl acetate	4.5%
Cocamidopropyl betaine	1.0%
Polyoxyethylene 23 lauryl ether	5.0%
Purified water	56.65%

9. A composition of Claim 5 comprising the following components:

Components	% w/w
Polawax A.31 (emulsifying wax NF ethoxylated stearyl alcohol with emulsifying agents)	2.0%
Alcohol USP	15.0%
Propylene glycol	10.0%
1,3 Butylene glycol	30.0%
Hydroxypropylmethylcellulose	0.2%

Minoxidil	2.0%
Purified water	42.8%

10. A composition of Claim 5 comprising the following components:

Components	% w/w
Propylene glycol	25.0%
Alcohol USP	20.0%
Polyoxyethylene 23 lauryl ether	5.0%
Minoxidil	2.0%
Purified water	48.0%

11. A composition of Claim 5 comprising the following components:

Components	% w/w
Propylene glycol	30.0
Alcohol USP	20.0
Minoxidil	2.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Cocamidopropyl betaine	0.5
Isostearyl alcohol	0.5
Purified water	46.0

12. A composition of Claim 5 comprising the following components:

Components	% w/w
Propylene glycol	30.0
Alcohol USP	20.0
Minoxidil	2.0
Oleth-10	2.0
Purified water	46.0

13. A composition of Claim 5 comprising the following components:

Components	% w/w
Propylene glycol	50.0
Alcohol USP	20.0
Minoxidil	5.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Cocamidopropyl betaine	0.5

Isostearyl alcohol	0.5
Purified water	23.0

14. A composition of Claim 5 comprising the following components:

Components	% w/w
Propylene glycol	50.0
Alcohol USP	20.0
Minoxidil	5.0
Oleth-10	3.0
Cocamidopropylbetaine	1.0
Purified water	21.0

15. A composition of CLaim 5 comprising the following components:

Components	% w/w
Propylene glycol	10.0
Butylene glycol	15.0
Alcohol USP	20.0
POE (23) lauryl ether	0.5
POE (2) stearyl ether	0.5
Isostearyl alcohol	0.5
Minoxidil	2.0
Purified water	50.0

16. A composition of Claim 1, comprising the following components:

Components	% w/w
Minoxidil	2%
Propylene glycol	20%
Alcohol USP	46.5%
Polawax A-31 or Reg	4%
Span 60	3%
Tween 80	3%
Hydroxypropyl methylcellulose USP	1.5%
Purified Water USP	20%

INTERNATIONAL SEARCH REPORT

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I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

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II. FIELDS SEARCHED

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Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 4139619 (C.A. CHIDSEY) 13 February 1979 see examples 1,7; claims cited in the application	1-16
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Y	EP, A, 0188793 (RICHARDSON-VICKS) 30 July 1986 see pages 8-19; table 1; example 2; claims	1,4,5,8-16
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* Special categories of cited documents: [10]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11th December 1987	28 JAN 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8702265 SA 18804

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/01/88
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4139619	13-02-79	US-A- 4596812	24-06-86
EP-A- 0188793	30-07-86	AU-A- 5080985	26-06-86
		JP-A- 61180709	13-08-86

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